Minutes of Meeting

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee

May 12, 2010

Members Present: Chair, Dr. Lucy Culpepper, Ms. Janet Allen, Dr. Gerard Ferris, Dr. Michelle Freeman, Dr. Kelli Littlejohn, Mr. Ben Main, Dr. Robert Moon, Ms. LaTonage Porter, Dr. Nancy Sawyer, Dr. Joseph Thomas and Dr. Chivers Woodruff

Members Absent: None

Presenters: Dr. Tina Hisel

Presenters Present via teleconference: Dr. Laureen Biczak

1. OPENING REMARKS

Dr. Culpepper called the Pharmacy and Therapeutics (P&T) Committee Meeting to order at 9:04 a.m.

2. APPROVAL OF MINUTES

Chairman Culpepper asked if there were any corrections to the minutes from the February 10, 2010 P&T Committee Meeting.

There were no objections. Mr. Main made a motion to approve the minutes as presented and Dr. Woodruff seconded to approve the minutes. The minutes were unanimously approved.

3. PHARMACY PROGRAM UPDATE

Dr. Littlejohn noted that a routine Preferred Drug List (PDL) update was completed on April 1, 2010.

Effective April 13, 2010, the Agency began accepting the Usual & Customary amount on pharmacy point-of-sale claims. An alert was sent to providers on March 31, 2010.

State FY2011 budget was signed into legislation by the Governor, including the portion that funds the Alabama Medicaid Agency. There were no prescription limit or brand limit changes made to the current policy. The Agency will still allow up to 5 brand drugs, as well as unlimited OTC and generic drugs per recipient.

The pharmacy reimbursement modification, in which the Agency is moving to an average acquisition cost pharmacy-based reimbursement, was signed into the budget legislation by the Governor. The Agency has been working with State pharmacy associations and has also coordinated informally with CMS. The Agency will be submitting an official State plan amendment and administrative code change for the pharmacy reimbursement modification. The Agency is also beginning to explore options for Phase 3. One possible option is the inclusion of pharmacies into a " medical neighborhood" concept. A meeting will be convened this summer and more information will be forthcoming.

The Patient Protection and Affordable Care Act (PPACA) was signed into legislation on March 23, 2010 and there are several changes that will affect Medicaid. The Agency is anticipating increased enrollment by 2014. There are several changes in the PPACA which will affect Pharmacy Services, including: 1) mandatory pharmacy coverage will be required for adult recipients by 2014; and 2) modifications to the federal rebate program, which will be retroactively implemented (January 2010).

CMS released guidance that several pancreatic enzymes no longer meet criteria for the federal rebate program, which means they are no longer covered. Therefore, several NDCs have been removed from the covered list.

Effective July 1, 2010, the NDC will be mandatory on all physician-administered drugs billed either electronically or on paper CMS-1500 or UB-04 claim forms. Claims will be rejected if the NDC is not included. An ALERT was sent to providers in January 2010 to address physician-administered drugs.

The Agency is releasing two RFIs (Request for Information). On May 17, 2010, a postcard will be mailed to potential vendors and provider associations. One of the RFIs is regarding Health Information Technology (HIT) and the second RFI is regarding the delivery and/or financing of healthcare for Medicaid recipients.

4. ORAL PRESENTATIONS BY MANUFACTURERS/MANUFACTURERS' REPRESENTATIVES

Five-minute verbal presentations were made on behalf of pharmaceutical manufacturers. The process and timing system for the manufacturers' oral presentations was explained. The drugs and corresponding manufacturers are listed below with the appropriate therapeutic class. There were a total of six manufacturer verbal presentations at the meeting.

5. PHARMACOTHERAPY CLASS REVIEWS (Please refer to the website for full text reviews.)

The pharmacotherapy class reviews began at approximately 9:15 a.m. There was one new drug class review.

First Generation Antihistamines: Ethanolamine Derivatives, American Hospital Formulary Service (AHFS) 040404, Ethylenediamine Derivatives, AHFS 040408, and Propylamine Derivatives, AHFS 040420

Manufacturer comments on behalf of these products:

None

Dr. Hisel commented that these agents are classified as first generation and second generation agents. First generation antihistamines bind to both central and peripheral H1-receptors, whereas second generation agents are more selective for peripheral H1-receptors.1 As a result, the first generation antihistamines may cause sedation, performance impairment in school and driving, as well as anticholinergic effects.

The first generation antihistamines are further classified as ethanolamine derivatives, ethylenediamine derivatives and propylamine derivatives. They are available as single entity agents, as well as in combination with other first generation antihistamines and oral decongestants. This review encompasses all systemic dosage forms. The eye, ear, nose, and throat (EENT) antiallergic agents were previously reviewed and are not included in this review. The majority of the first generation antihistamines are available in a generic formulation and several agents are also available over-the-counter. Cough and cold products are an excludable/optional drug class in accordance with the Omnibus Budget Reconciliation Act of 1990 (OBRA 90). Brand cough and cold products are not covered by Alabama Medicaid; therefore, these products were not included in this review. The second generation antihistamines are not included on the mandatory preferred drug list. Only brand products currently require prior authorization, whereas covered generics and over-the-counter products (unless otherwise specified) do not require prior authorization. Although the second generation antihistamines may be mentioned throughout this review, they are not being considered for preferred status at this time.

Current treatment guidelines that incorporate the use of the first generation antihistamines are summarized in Table 2. There are a variety of therapeutic options for the management of allergic rhinitis, which includes the use of first generation antihistamines. In general, the second generation antihistamines are preferred over first generation agents because they have a lower tendency to cause sedation, anticholinergic effects and performance impairment. For the treatment of urticaria, antihistamines are the cornerstone of therapy. Second generation antihistamines are generally preferred. For the treatment of atopic dermatitis, topical corticosteroids are the standard of care. Antihistamines may help relieve pruritic symptoms, especially in those with concomitant urticaria or allergic rhinitis. First generation antihistamines may also be useful in patients with sleep disturbances due to pruritus. For the management of allergic/atopic conjunctivitis, topical antihistamines are an effective treatment option; however, oral antihistamines may also be considered. The available guidelines do not give preference to one particular first generation antihistamine over another.

There are very few studies that directly compare the first generation antihistamines. Clemastine and chlorpheniramine were found to be equally effective for the treatment of allergic rhinitis. The first generation antihistamines have also been shown to be as effective as second generation antihistamines in multiple studies. The fixed-dose combination of triprolidine/pseudoephedrine was shown to be more effective than monotherapy with triprolidine or pseudoephedrine. However,

there were no studies found in the medical literature that compared the efficacy of the fixed-dose combination product to the coadministration of each component as separate formulations. Several clinical trials have evaluated the central nervous system effects of the first generation antihistamines. The second generation antihistamines have been shown to adversely affect cognitive and psychomotor functions, as well as impair driving performance.

Dr. Hisel concluded that there is insufficient evidence to support that one brand first generation antihistamine is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand first generation antihistamines within the class reviewed are comparable to each other and to the generics and OTC products in the class and offer no significant clinical advantage over other alternatives in general use.

No brand first generation antihistamine is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

There were no further discussions on the agents in this class. Dr. Culpepper asked the P&T Committee Members to mark their ballots.

6. PHARMACOTHERAPY CLASS RE-REVIEWS (Please refer to the website for full text reviews.)

There were a total of ten drug class re-reviews. The estrogens and diabetic agents were last reviewed in February 2008.

Estrogens: AHFS 681604
Manufacturer comments on behalf of these products:
None

Dr. Hisel commented that the products that are included in this review are listed in Table 1. They are available in a variety of dosage forms, including injectable, oral, topical, transdermal and vaginal preparations. Estradiol, estradiol valerate, estradiol/norethindrone and estropipate are available in a generic formulation.

Current treatment guidelines that incorporate the use of the estrogens are summarized in Table 2, several of which have been updated since this class was last reviewed. The use of hormone therapy was associated with an increased risk of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli and deep vein thrombosis in the Women's Health Initiative study. The use of hormone therapy is not recommended for the prevention of chronic diseases, such as cardiovascular disease, cerebrovascular disease or dementia. Hormone therapy may be considered for the prevention of osteoporosis when other therapies are not appropriate or when the benefits outweigh the risks. Hormone therapy remains the most effective treatment for moderate-to-severe menopausal symptoms. It is recommended that the lowest possible dose be used for the shortest

amount of time. Vaginal formulations are recommended for women who only have symptoms of vulvar and vaginal atrophy. Several progestational agents have been shown to provide endometrial protection, including medroxyprogesterone, drospirenone, levonorgestrel, norethindrone and norgestimate.

Numerous studies have demonstrated a similar improvement in menopausal symptoms with the various estrogen preparations. Dr. Hisel concluded that there is insufficient evidence to support that one brand estrogen is safer or more efficacious than another.

Therefore, all brand estrogens within the class reviewed are comparable to each other and to the generics and offer no significant clinical advantage over other alternatives in general use.

No brand estrogen is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

There was no further discussion on the agents in this class. Dr. Culpepper asked the P&T Committee Members to mark their ballots.

Dr. Hisel commented that the antidiabetic agents are categorized into 9 different AHFS subclasses, which will be reviewed individually. The prescribing information for all of the oral agents and the injectable incretin mimetics have been updated with regards to their FDA-approved indications. They are all approved for use as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus. Specific information regarding their use as monotherapy, dual therapy, triple therapy, or in combination with insulin is included in the dosing and administration section, as well as in the clinical trials section of the prescribing information. Several guidelines have been updated since these classes were last reviewed. This includes the treatment algorithm published jointly by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD), the algorithm published by the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE), as well as others. For the treatment of type 2 diabetes, metformin is consistently recommended as first-line therapy across all of the guidelines and it is the cornerstone of combination therapy due to its efficacy and safety. Updated guideline recommendations regarding the use of the other oral agents will be discussed briefly during each class review.

Alpha-Glucosidase Inhibitors: AHFS 682002

Manufacturer comments on behalf of these products:
None

Dr. Hisel commented that the alpha-glucosidase inhibitors that are included in this review are listed in Table 1. A generic formulation of acarbose has been approved by the FDA since this class was last reviewed.

The alpha-glucosidase inhibitors were not specifically included in the ADA/EASD treatment algorithm. According to the AACE/ACE algorithm, the alpha-glucosidase inhibitors are appropriate for use as monotherapy in patients with an A1C between 6.5% and 7.5%; however, the

metformin is the cornerstone of therapy in this A1C range because of its safety and efficacy. The alpha-glucosidase inhibitors are not recommended for use in patients with higher A1Cs due to their limited glucose-lowering potential. The available guidelines do not give preference to one alpha-glucosidase inhibitor over another.

A variety of clinical trials have been conducted with the alpha-glucosidase inhibitors. There were no studies found in the medical literature that directly compared acarbose and miglitol. The majority of the clinical trials have compared active treatment to placebo or compared combination therapy to monotherapy. In these studies, the more aggressive treatment regimens improved glycemic parameters to a greater extent than the less-intensive treatment regimens. When comparing similar monotherapy treatment regimens, sulfonylureas have been shown to be more effective than the alpha-glucosidase inhibitors.

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with the alpha-glucosidase inhibitors.

Therefore, all brand alpha-glucosidase inhibitors within the class reviewed are comparable to each other and to the generics and OTC products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

No brand alpha-glucosidase inhibitor is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

There were no further discussions on the agents in this class. Dr. Culpepper asked the P&T Committee Members to mark their ballots.

Amylinomimetics: AHFS 682003

Manufacturer comments on behalf of these products:
None

Dr. Hisel commented that pramlintide is the only amylinomimetic agent that is currently available. It is approved for use as an adjunctive treatment in patients with type 1 and type 2 diabetes who use mealtime insulin therapy and who have failed to achieve desired glucose control despite optimal insulin therapy. It is not available in a generic formulation.

With the treatment of Type 2 diabetes, pramlintide was not specifically included in the ADA/EASD treatment algorithm. According to the AACE/ACE algorithm, the use of pramlintide in combination with insulin may be considered for patients with type 2 diabetes with an A1C between 7.5% and 9% and persistent postprandial hyperglycemia. Other guidelines either do not discuss the use of pramlintide for the treatment of type 2 diabetes, or consider it an alternative treatment option. For the treatment of type 1 diabetes, the ADA recommends the use of multiple dose insulin injections or continuous subcutaneous insulin infusion therapy and does not provide recommendations regarding the use of pramlintide in this patient population.

Several clinical trials have been conducted with pramlintide in patients with type 1 and type 2 diabetes. Pramlintide has been shown to improve glycemic control in patients who are already on insulin compared to placebo.

Pramlintide does not cause hypoglycemia when used alone; however, it is intended to be coadministered with insulin therapy. In this setting, pramlintide increases the risk of insulin-induced severe hypoglycemia, especially in patients with type 1 diabetes mellitus. According to the prescribing information, therapy should only be considered in patients with insulin-using type 1or type 2 diabetes who have failed to achieve adequate glycemic control despite individualized insulin management and in patients who are receiving ongoing care under the guidance of a healthcare professional skilled in the use of insulin and supported by the services of diabetes a educator.

Since pramlintide is only approved for use as an adjunctive treatment in patients with type 1 and type 2 diabetes, it should be managed through the existing medical justification portion of the prior authorization process.

No brand amylinomimetic is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

Dr. Sawyer asked whether pramlintide had significant utilization in Alabama. Dr. Littlejohn replied that the drug is covered and that there has been occasional utilization to date.

Dr. Culpepper requested that Committee members state their name for the record before asking a question.

There were no further discussions on the agents in this class. Dr. Culpepper asked the P&T Committee Members to mark their ballots.

Biguanides: AHFS 682004

Manufacturer comments on behalf of these products:
None

Dr. Hisel commented that metformin in the only biguanide that is currently available. The immediate-release and sustained-release tablets are both available in a generic formulation.

Metformin is consistently recommended as first-line therapy and it is the cornerstone of combination therapy. Guidelines do not give preference to one particular metformin formulation over another. Numerous clinical trials have established the efficacy/safety of metformin as monotherapy, as well as in combination with other antidiabetic agents. Studies directly comparing immediate-release and sustained-release formulations of metformin have demonstrated similar efficacy.

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with metformin. Dr. Hisel concluded that there is insufficient evidence to support that one brand metformin product is safer or more efficacious than another.

Therefore, all brand biguanides within the class reviewed are comparable to each other and to the generics and offer no significant clinical advantage over other alternatives in general use.

No brand biguanide is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

Dr. Ferris stated that one of the actions of metformin is to reduce nocturnal glucose secretion. He has seen a number of patients that are on a twice-daily dose of metformin. He thought that the dose could be combined into a single bedtime dose to increase efficacy. He asked if that was a correct assumption. Dr. Hisel replied that the immediate-release metformin formulations are generally given several times per day, while the extended-release preparations are dosed once-daily. She was not aware of studies specifically investigating the use of the immediate-release products dosed solely in the evening. She commented that metformin primarily reduces hepatic glucose production; however, it may also improve peripheral glucose utilization within the muscle. Administering it more than once daily may have additional effects despite the pharmacologic effects within the liver.

Dr. Sawyer asked if prior authorization as required to use metformin for polycystic ovarian syndrome. Dr. Littlejohn replied that generic products are preferred and there are no requirements for a diagnosis on a prescription.

There were no further discussions on the agents in this class. Dr. Culpepper asked the P&T Committee Members to mark their ballots.

Dipeptidyl Peptidase-4 (DPP-4) Inhibitors: AHFS 682005

Manufacturer comments on behalf of these products:
Januvia® - Merck
Janumet® - Merck
Onglyza® - Bristol Myers Squibb

Dr. Hisel commented that the DPP-4 inhibitors that are included in this review are listed in Table 1. Sitagliptin is available as a single entity agent and as a fixed-dose combination product with metformin. Saxagliptin was approved by the FDA since this class was last reviewed and information on this product has been added to the review. There are no generic products available.

The DPP-4 inhibitors were not specifically included in the ADA/EASD treatment algorithm. According to the AACE/ACE algorithm, the DPP-4 inhibitors are appropriate for use as monotherapy in patients with an A1C between 6.5% and 7.5% due to their minimal risk of hypoglycemia. However, metformin is the cornerstone of therapy due to its safety and efficacy. An incretin mimetic or a DPP-4 inhibitor is the preferred second agent to use in combination with metformin regardless of the A1C range; however, the incretin mimetics are given a higher priority than DPP-4 inhibitors due to their greater effect on reducing postprandial glucose and potential for weight loss. Other guidelines do not address the use of the DPP-4 inhibitors or recommend them as a second- or third-line treatment option.

A variety of clinical trials have been conducted with the DPP-4 inhibitors. There were no studies found in the medical literature that directly compared saxagliptin and sitagliptin. The majority of the clinical trials have compared active treatment to placebo or compared combination therapy to monotherapy. In these studies, the more aggressive treatment regimens improved glycemic parameters to a greater extent than the less-intensive treatment regimens. In treatment naïve patients, sitagliptin was shown to be non-inferior to metformin when used as monotherapy. Sitagliptin was also shown to be as effective as rosiglitazone or glipizide when these agents were added to existing metformin monotherapy. The addition of exenatide to metformin led to a greater reduction in 2-hour postprandial glucose concentrations compared to the addition of sitagliptin to metformin.

The DPP-4 inhibitors are generally well tolerated. There have been postmarketing reports of serious hypersensitivity reactions in patients taking sitagliptin. These reactions include anaphylaxis, angioedema and exfoliative skin conditions including Stevens-Johnson syndrome. There have also been postmarketing reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, in patients taking sitagliptin. Saxagliptin is relatively new to the market and these specific adverse events are not listed in the prescribing information for this product.

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with the DPP-4 inhibitors. Dr. Hisel concluded that there is insufficient evidence to support that one brand DPP-4 inhibitor is safer or more efficacious than another.

Therefore, all brand DPP-4 inhibitors within the class reviewed are comparable to each other and to the generics and OTC products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

No brand DPP-4 inhibitor is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

Mr. Main asked if the DPP-4 inhibitors were considered second-line therapy. Dr. Hisel replied that, according to the recent AACE/ACE algorithm, the DPP-4 inhibitors are recommended as second-line therapy in combination with metformin.

There were no further discussions on the agents in this class. Dr. Culpepper asked the P&T Committee Members to mark their ballots.

Incretin Mimetics: AHFS 682006

Manufacturer comments on behalf of these products:
None

Dr. Hisel commented that exenatide is the only incretin mimetic included in this review. Liraglutide is also an incretin mimetic, which was approved by the FDA for the treatment of type 2 diabetes in January 2010. However, it was not included in this review because Alabama Medicaid's policy states

that drugs must be commercially available for a minimum of 180 days to be eligible for inclusion in a PDL review. There are no generic products in this class.

According to the ADA/EASD treatment algorithm, metformin is recommended as first-line therapy, followed by the addition of insulin or a sulfonylurea. However, the addition of exenatide or pioglitazone to metformin may be considered if hypoglycemia is a concern. According to the AACE/ACE algorithm, an incretin mimetic or a DPP-4 inhibitor is the preferred second agent to use in combination with metformin; however, the incretin mimetics are given a higher priority than DPP-4 inhibitors due to the greater effect on reducing postprandial glucose and potential for weight loss. The incretin mimetics are recommend as a second- or third-line treatment option in other guidelines.

A variety of clinical trials have been conducted with exenatide. Several clinical trials have compared active treatment to placebo or compared combination therapy to monotherapy. In these studies, the more aggressive treatment regimens improved glycemic parameters to a greater extent than the less-intensive treatment regimens. In a comparative study, the addition of exenatide to metformin led to a greater reduction in postprandial glucose concentrations compared to the addition of sitagliptin to metformin. Exenatide was shown to be as effective as insulin glargine and insulin aspart in patients receiving concurrent treatment with other oral antidiabetic agents. In a separate study, the addition of biphasic insulin aspart 70/30 to metformin and sulfonylurea therapy led to better improvements in glycemic control in patients with high baseline A1C values (~10%) compared to the addition of exenatide.

There have been postmarketing reports of acute pancreatitis in patients taking exenatide. There have also been postmarketing reports of altered renal function, including increased serum creatinine, renal impairment, worsened chronic renal failure and acute renal failure, sometimes requiring hemodialysis or kidney transplantation. Patients may develop antibodies to exenatide consistent with the potentially immunogenic properties of protein and peptide pharmaceuticals.

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with exenatide. Since exenatide is not recommended as first-line therapy for the treatment of type 2 diabetes, it should be managed through the medical justification portion of the prior authorization process.

No brand incretin mimetic is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

There were no further discussions on the agents in this class. Dr. Culpepper asked the P&T Committee Members to mark their ballots.

Insulins: AHFS 682008

Manufacturer comments on behalf of these products:
Novolog® - Novo Nordisk
Novolog Mix 70/30® - Novo Nordisk
Levemir® - Novo Nordisk

Dr. Hisel commented that the insulins that are included in this review are listed in Table 1. There are two types of insulin preparations currently available: human insulin and insulin analogs. They are categorized based on their duration of action, which includes rapid-acting, short-acting, intermediate-acting and long-acting insulins. There are no generic products available; however, some insulins are available over-the-counter.

For the treatment of type 1 diabetes mellitus, the ADA and AACE guidelines recommend the use of basal-bolus therapy consisting of 3 to 4 injections of basal and prandial insulin per day, or continuous subcutaneous insulin infusion with an insulin pump. The insulin analogs are preferred over human insulin because they are associated with fewer hypoglycemic episodes. The guidelines do not give preference to one particular insulin analog over another for the treatment of type 1 diabetes mellitus.

According to the ADA/EASD algorithm for the treatment of type 2 diabetes, if metformin fails to achieve glycemic goals, insulin or a sulfonylurea should be added. Insulin therapy can be initiated with a basal regimen using an intermediate- or long-acting insulin preparation. If treatment needs to be intensified, short- or rapid-acting insulins can be added before meals. According to the AACE/ACE algorithm, insulin therapy can be initiated with basal, premixed, prandial, or basal-bolus regimens; however, long-acting basal insulin is generally the initial choice. Insulin glargine and insulin detemir are preferred over NPH insulin because they have a lower risk of hypoglycemia. If treatment needs to be intensified, the use of premixed insulin analogs can be considered. Other guidelines recommend the use of either human insulin or insulin analogs when patients require insulin therapy. The available guidelines do not give preference to one particular insulin analog over another for the treatment of type 2 diabetes.

For the treatment of type 1 diabetes the use of rapid-acting insulin analogs has resulted in a similar, or greater, reduction in A1C compared to regular insulin. The rate of hypoglycemia was found to be either similar, or lower, with the rapid-acting insulin analogs compared to regular insulin. Only one study was found in the medical literature that directly compared insulin glulisine and insulin lispro as prandial therapy, while maintaining stable therapy with insulin glargine. There was a similar reduction in A1C after 26 weeks of therapy and the rates of hypoglycemia did not differ among the treatment groups. Other studies have evaluated the efficacy and safety of various basal insulin regimens, while maintaining stable prandial therapy. The use of long-acting insulin analogs has resulted in a similar, or greater, reduction in A1C compared to NPH insulin. The rate of hypoglycemia was found to be either similar, or lower, with the long-acting insulin analogs compared to NPH insulin. Two trials directly compared insulin detemir and insulin glargine as basal therapy, while maintaining stable therapy with insulin aspart. There was a similar reduction in A1C reported in both studies and the overall rates of hypoglycemia did not differ among the treatment groups. However, nocturnal hypoglycemia was significantly lower with insulin detemir (reported in only one study). Two studies compared insulin aspart and insulin lispro administered through a continuous subcutaneous insulin infusion (CSII). There was no difference in A1C at the end of the 16-week trials and the rates of hypoglycemia were similar among the treatment groups.

For the treatment of type 2 diabetes mellitus, several studies have compared the efficacy and safety of insulin therapy alone, or in combination with oral agents. The use of rapid-acting insulin analogs

has resulted in a similar, or greater, reduction in A1C compared to regular insulin. There was no difference in hypoglycemic episodes reported among the treatment groups. The majority of the studies comparing long-acting insulin analogs to NPH have demonstrated similar reductions in A1C. However, the long-acting insulin analogs were associated with less hypoglycemia than NPH insulin. Two studies directly compared insulin detemir with insulin glargine and showed no difference in A1C after 52 weeks of treatment. A third study reported a greater reduction in A1C with insulin glargine than insulin detemir after 26 weeks of therapy There was no difference in the risk of overall hypoglycemia in any of the studies. In a study comparing biphasic insulin lispro (75/25 mix) and biphasic insulin aspart (70/30 mix), there was no significant difference in A1C or overall hypoglycemia reported among the treatment groups.

Dr. Hisel concluded that the insulin analogs have been shown to be at least as effective, or more effective, than human insulin. In several studies, there was a lower risk of hypoglycemia with the insulin analogs compared to human insulin. Guidelines recommend the use of insulin analogs in patients with type 1 diabetes mellitus. For the treatment of type 2 diabetes, metformin is recommended as first-line therapy. When insulin therapy is warranted, either an insulin analog or human insulin may be used. There is insufficient evidence to conclude that one rapid-acting insulin analog is safer or more efficacious than another. There is also insufficient evidence to conclude that one long-acting insulin analog is safer or more efficacious than another.

Therefore, all brand products within the class reviewed, with the exception of rapid-acting and long-acting insulin analogs, are comparable to each other and to the generics and OTC products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use. Rapid-acting insulin analogs offer significant clinical advantages in general use over short-acting human insulin, but are comparable to each other. Long-acting insulin analogs offer significant clinical advantages over intermediate-acting human insulin, but are comparable to each other.

No brand insulin, with the exception of rapid-acting and long-acting insulin analogs, is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

Alabama Medicaid should work with manufacturers on cost proposals so that at least one brand rapid-acting insulin analog is selected as a preferred agent.

Alabama Medicaid should work with manufacturers on cost proposals so that at least one brand long-acting insulin analog is selected as a preferred agent.

Dr. Ferris asked for clarification regarding which combination insulin products are on the PDL. Dr. Hisel referred the Committee members to Table 1. She stated that Humulin® 50/50, Humulin® 70/30 and Novolin® 70/30 are preferred combination products. Dr. Ferris asked if their preferred status may change. Dr. Hisel commented that they are covered OTC products; therefore, their PDL status should not change.

Dr. Culpepper commented that there are two long-acting insulins on the PDL as well. The recommendation is that Medicaid select at least one long-acting insulin as a preferred agent.

Dr. Culpepper reminded the Committee members that there were three recommendations on their ballot.

Dr. Woodruff asked for clarification regarding which insulin products are available OTC. Dr. Hisel stated that there is a symbol in Table 1 indicating which products are available OTC. Currently, Humulin® R, Novolin® R, Humulin® N, Novolin® N, Humulin® 50/50, Humulin® 70/30, and Novolin® 70/30 insulins are available OTC.

There were no further discussions on the agents in this class. Dr. Culpepper asked the P&T Committee Members to mark their ballots.

Meglitinides: AHFS 682016

Manufacturer comments on behalf of these products:
None

Dr. Hisel commented that the meglitinides that are included in this review are listed in Table 1. Repaglinide is available as a single entity agent and as a fixed-dose combination product with metformin. Nateglinide is available in a generic formulation; metformin is also available generically in a separate formulation.

The meglitinides were not specifically included in the ADA/EASD treatment algorithm. According to the AACE/ACE algorithm, the use of an insulin secretagogue (sulfonylurea or meglitinide) is not recommended in patients with an A1C between 6.5% and 7.5% as monotherapy due to the risk of hypoglycemia and weight gain. The meglitinides may be considered for dual or triple therapy in this A1C range; however, the incretin mimetics and DPP-4 inhibitors are given higher priority. For patients with an A1C of 7.6% to 9.0%, sulfonylureas and meglitinides are in the lowest recommended position due to the risk of hypoglycemia. There is also a need for the greater glucose-lowering efficacy of sulfonylureas in this A1C range; therefore, they are positioned before the meglitinides. The meglitinides are recommended as a second- or third-line treatment option in other guidelines. The available guidelines do not give preference to one meglitinide over another.

The meglitinides have been studied in a variety of clinical trials. Three studies have directly compared nateglinide and repaglinide, either as monotherapy or in combination with metformin. In all 3 studies, the mean change in A1C from baseline was significantly greater with repaglinide compared to nateglinide. The meglitinides have also been compared to sulfonylureas in monotherapy studies. Glyburide was found to be more effective than nateglinide in one study, whereas glyburide and repaglinide were found to be equally efficacious in another study. The combination of nateglinide and metformin was shown to be as effective, or more effective, than the combination of glyburide and metformin in two studies. Several studies evaluated the efficacy of meglitinides in dual therapy regimens compared to monotherapy regimens. In these studies, the more aggressive treatment regimens improved glycemic parameters to a greater extent than the less-intensive treatment regimens.

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with the meglitinides. Since the meglitinides are not recommended as first-line therapy for the treatment of type 2 diabetes mellitus, formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

No brand meglitinide is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

There were no further discussions on the agents in this class. Dr. Culpepper asked the P&T Committee Members to mark their ballots.

Sulfonylureas: AHFS 682020

Manufacturer comments on behalf of these products:
None

Dr. Hisel commented that the sulfonylureas that are included in this review are listed in Table 1. They are available as single entity agents and as fixed-dose combinations with metformin. All of the sulfonylureas are available in a generic formulation, including the fixed-dose combination products.

According to the ADA/EASD treatment algorithm, metformin is recommended as first-line therapy, followed by the addition of insulin or a sulfonylurea (except glyburide or chlorpropamide). Insulin is more effective for patients with an A1C >8.5% or with symptoms secondary to hyperglycemia. According to the AACE/ACE algorithm, the use of an insulin secretagogue (sulfonylurea or meglitinide) is not recommended in patients with an A1C between 6.5% and 7.5% as monotherapy due to the risk of hypoglycemia and weight gain. The sulfonylureas may be considered for dual or triple therapy in this A1C range; however, the incretin mimetics and DPP-4 inhibitors are given higher priority. For patients with an A1C of 7.6% to 9.0%, sulfonylureas and meglitinides are in the lowest recommended position due to the risk of hypoglycemia. Sulfonylureas are positioned before the meglitinides due to the need for the greater glucose-lowering efficacy of the sulfonylureas in this A1C range. For patients with an A1C of >9%, a sulfonylurea may be added as a third-line agent. Other guidelines recommend the use of a sulfonylurea as a second-line treatment option. In general, the guidelines do not give preference to one sulfonylurea over another.

The sulfonylureas have been evaluated in numerous clinical trials. In monotherapy studies, glipizide and glyburide were found to be equally efficacious, regardless of the dosage form used. Sulfonylureas have been shown to be more effective than alpha-glucosidase inhibitors. Several studies evaluated the efficacy of sulfonylureas in dual therapy regimens compared to monotherapy regimens. In these studies, the more aggressive treatment regimens improved glycemic parameters to a greater extent than the less-intensive treatment regimens. However, in studies that directly compared various dual therapy regimens, there were no differences in efficacy noted.

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with the sulfonylureas. There is insufficient evidence to support that one brand

sulfonylurea is more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand sulfonylureas within the class reviewed are comparable to each other and to the generics and OTC products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

No brand sulfonylurea is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

There were no further discussions on the agents in this class. Dr. Culpepper asked the P&T Committee Members to mark their ballots.

Thiazolidinediones: AHFS 682028

Manufacturer comments on behalf of these products:
None

Dr. Hisel commented that the thiazolidinediones that are included in this review are listed in Table 1. They are available as single entity agents and as fixed-dose combinations with metformin or glimepiride. There are no generic products available; however, metformin and glimepiride are available generically in a separate formulation.

According to the ADA/EASD treatment algorithm, metformin is recommended as first-line therapy, followed by the addition of insulin or a sulfonylurea. According to the AACE/ACE algorithm, thiazolidinediones are appropriate for use as monotherapy in patients with an A1C between 6.5% and 7.5% due to their minimal risk of hypoglycemia. However, metformin is the cornerstone of therapy. An incretin mimetic or a DPP-4 inhibitor is the preferred second agent to use in combination with metformin. The thiazolidinediones may also be considered for dual or triple therapy, but they are positioned lower than incretin mimetics and DPP-4 inhibitors due to the risk of weight gain, fluid retention, congestive heart failure and fractures.

A variety of clinical trials have been conducted with the thiazolidinediones. In comparative studies, the use of pioglitazone and rosiglitazone led to similar improvements in glycemic control. Several studies evaluated the efficacy of thiazolidinediones in dual therapy regimens compared to monotherapy regimens. In these studies, the more aggressive treatment regimens improved glycemic parameters to a greater extent than the less-intensive treatment regimens. In studies that directly compared various dual therapy regimens, there were no differences in efficacy noted. The thiazolidinedione fixed-dose combination products have been shown to be improve glycemic control in patients with type 2 diabetes. However, there were no randomized studies found in the medical literature that directly compared the efficacy of the fixed-dose combination products to the coadministration of each component as separate formulations.

Thiazolidinediones may cause weight gain and fluid retention, as well as increase the risk for congestive heart failure and fractures. The cardiovascular safety of rosiglitazone has been a controversial issue since 2007. The results of two cardiovascular outcomes studies with the

thiazolidinediones have been reported (PROactive and RECORD); however, neither study directly compared pioglitazone and rosiglitazone. A variety of meta-analyses have been conducted by independent investigators to assess the link between the use of thiazolidinediones and cardiovascular events. Currently, the prescribing information for pioglitazone and rosiglitazone differ with regards to myocardial ischemic events; however, other safety issues are similar. The ADA/EASD algorithm and ICSI guidelines recommend the use of pioglitazone over rosiglitazone, whereas the AACE/ACE algorithm and NICE guidelines do not give preference to one thiazolidinedione over another. In February 2010, the FDA notified healthcare professionals that it is reviewing the primary data from the RECORD trial to further assess the cardiovascular risks with rosiglitazone. They stated that there are no new conclusions or recommendations about the use of rosiglitazone in the treatment of type 2 diabetes. The FDA recommends that healthcare professionals continue to follow the recommendations in the prescribing information when using rosiglitazone. A new study is currently underway (Thiazolidinedione Intervention With Vitamin D Evaluation; TIDE), which will evaluate the cardiovascular effects of long-term treatment with rosiglitazone or pioglitazone in patients with type 2 diabetes who have a history of, or are at risk for, cardiovascular disease.

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with the thiazolidinediones. Due to the absence of long-term comparative studies, firm conclusions about the cardiovascular risks associated with pioglitazone and rosiglitazone cannot be made. There is insufficient evidence to support that one brand thiazolidinedione is more efficacious than another. Since these agents are not recommended as first-line therapy for the treatment of type 2 diabetes mellitus, the thiazolidinediones should be managed through the medical justification portion of the prior authorization process.

No brand thiazolidinedione is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

There were no further discussions on the agents in this class. Dr. Culpepper asked the P&T Committee Members to mark their ballots.

7. RESULTS OF VOTING ANNOUNCED

The results of voting were announced and all classes were approved as recommended. Results of voting are described in the Appendix to the minutes.

8. NEW BUSINESS

There was no new business.

9. NEXT MEETING DATE

The next P&T Committee Meetings are scheduled for 9:00 a.m. on August 11, 2010 and November 10, 2010 at the Medicaid Building in the Commissioner's Board Room.

10. ADJOURN

There being no further business, Dr. Thomas moved to adjourn, and Mr. Main seconded.

The meeting was adjourned at 10:25 a.m.

Appendix

RESULTS OF THE BALLOTING
Alabama Medicaid Agency
Pharmacy and Therapeutics Committee
May 12, 2010

A. **Recommendation:** No brand first generation antihistamine is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

Amendment: None

Vote: Unanimous to approve as recommended

_____ Medical Director	☐ Approve	☐ Approve as amended	☐ Disapprove	☐ No action
Kathy Kelly Deputy Commissioner	☑ Approve	☐ Approve as amended	☐ Disapprove	☐ No action
Carol H. Steckel Commissioner	☑ Approve	☐ Approve as amended	☐ Disapprove	☐ No action

B. **Recommendation:** No brand estrogen is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

Amendment: None

Vote: Unanimous to approve as recommended

_____ Medical Director	☐ Approve	☐ Approve as amended	☐ Disapprove	☐ No action
Kathy Kelly Deputy Commissioner	☑ Approve	☐ Approve as amended	☐ Disapprove	☐ No action
Carol H. Steckel Commissioner	☑ Approve	☐ Approve as amended	☐ Disapprove	☐ No action

C. **Recommendation:** No brand alpha-glucosidase inhibitor is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

Amendment: None

Vote: Unanimous to approve as recommended

_____ ☐ Approve ☐ Approve as amended ☐ Disapprove ☐ No action
Medical Director

Kathy Kelly ☑ Approve ☐ Approve as amended ☐ Disapprove ☐ No action
Deputy Commissioner

Carol H. Steckel ☑ Approve ☐ Approve as amended ☐ Disapprove ☐ No action
Commissioner

D. **Recommendation:** No brand amylinomimetic is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

Amendment: None

Vote: Unanimous to approve as recommended

_____ ☐ Approve ☐ Approve as amended ☐ Disapprove ☐ No action
Medical Director

Kathy Kelly ☑ Approve ☐ Approve as amended ☐ Disapprove ☐ No action
Deputy Commissioner

Carol H. Steckel ☑ Approve ☐ Approve as amended ☐ Disapprove ☐ No action
Commissioner

E. **Recommendation:** No brand biguanide is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

Amendment: None

Vote: Unanimous to approve as recommended

_____ ☐ Approve ☐ Approve as amended ☐ Disapprove ☐ No action
Medical Director

Kathy Hall ☑ Approve ☐ Approve as amended ☐ Disapprove ☐ No action
Deputy Commissioner

Carol H. Steckel ☑ Approve ☐ Approve as amended ☐ Disapprove ☐ No action
Commissioner

F. **Recommendation:** No brand DPP-4 inhibitor is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

Amendment: None

Vote: Unanimous to approve as recommended

_____ ☐ Approve ☐ Approve as amended ☐ Disapprove ☐ No action
Medical Director

Kathy Hall ☑ Approve ☐ Approve as amended ☐ Disapprove ☐ No action
Deputy Commissioner

Carol H. Steckel ☑ Approve ☐ Approve as amended ☐ Disapprove ☐ No action
Commissioner

G. **Recommendation:** No brand incretin mimetic is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

Amendment: None

Vote: Unanimous to approve as recommended

_____ ☐ Approve ☐ Approve as amended ☐ Disapprove ☐ No action
Medical Director

Kathy Kell ☑ Approve ☐ Approve as amended ☐ Disapprove ☐ No action
Deputy Commissioner

Carol H. Steckel ☑ Approve ☐ Approve as amended ☐ Disapprove ☐ No action
Commissioner

H. **Recommendation:** No brand insulin, with the exception of rapid-acting and long-acting insulin analogs, is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

Alabama Medicaid should work with manufacturers on cost proposals so that at least one brand rapid-acting insulin analog is selected as a preferred agent.

Alabama Medicaid should work with manufacturers on cost proposals so that at least one brand long-acting insulin analog is selected as a preferred agent.

Amendment: None

Vote: Unanimous to approve as recommended

_____ ☐ Approve ☐ Approve as amended ☐ Disapprove ☐ No action
Medical Director

Kathy Kell ☑ Approve ☐ Approve as amended ☐ Disapprove ☐ No action
Deputy Commissioner

Carol H. Steckel ☑ Approve ☐ Approve as amended ☐ Disapprove ☐ No action
Commissioner

I. **Recommendation:** No brand meglitinide is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

Amendment: None

Vote: Unanimous to approve as recommended

_____ ☐ Approve ☐ Approve as amended ☐ Disapprove ☐ No action
Medical Director

Kathy Hall ☑ Approve ☐ Approve as amended ☐ Disapprove ☐ No action
Deputy Commissioner

Carol H. Steckel ☑ Approve ☐ Approve as amended ☐ Disapprove ☐ No action
Commissioner

J. **Recommendation:** No brand sulfonylurea is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

Amendment: None

Vote: Unanimous to approve as recommended

_____ ☐ Approve ☐ Approve as amended ☐ Disapprove ☐ No action
Medical Director

Kathy Hall ☑ Approve ☐ Approve as amended ☐ Disapprove ☐ No action
Deputy Commissioner

Carol H. Steckel ☑ Approve ☐ Approve as amended ☐ Disapprove ☐ No action
Commissioner

K. Recommendation: No brand thiazolidinedione is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

Amendment: None

Vote: Unanimous to approve as recommended

_____ ☐ Approve ☐ Approve as amended ☐ Disapprove ☐ No action
Medical Director

Kathy Hall ☑ Approve ☐ Approve as amended ☐ Disapprove ☐ No action
Deputy Commissioner

Carol H. Steckel ☑ Approve ☐ Approve as amended ☐ Disapprove ☐ No action
Commissioner

Respectfully submitted,

Tina Hisel

Tina Hisel, Pharm.D., BCPS — May 12, 2010 Date